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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/535,556	09/26/95	FALO L	125350

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EXAMINER	
SCHMUCK, J	
ART UNIT	**PAPER NUMBER**
1819	

DATE MAILED: 03/18/97

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

FILE

Office Action Summary	Application No. 08/535,556	Applicant(s) Falo & Rock
	Examiner Jill Schmuck	Group Art Unit 1819

☒ Responsive to communication(s) filed on *Jan 10, 1997* .

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-67* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-67* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Response to Arguments

Applicants' arguments in the Amendment and the Falo Declaration under 37 CFR 1.132, both filed Jan. 10, 1997 have been fully considered but are not deemed persuasive.

1. The specification remains objected to under 35 U.S.C. §112, first paragraph.

Claims 1-67 remain rejected under 35 U.S.C. §112, first paragraph as set forth on pages 1-9 of the last Office action, because Applicants' arguments have not convinced the Examiner that one skilled in the art could use the claimed invention in a method of genetic immunization without undue experimentation and a reasonable expectation of success. Applicants assert that the references applied by the Examiner in this rejection are irrelevant or unsuitable in regard to the claimed invention (page 3 of the Amendment). However, the Examiner disagrees. Applicants failed to supply evidence that results obtained from the specific mouse tumor model disclosed in the specification can be used to extrapolate to results obtained in any human therapeutic procedure. Applicants failed to demonstrate the successful gene transfer and expression of any other antigenic proteins. It is not evident that similar results could be obtained from the same mouse tumor model using any other DNA encoding for an antigenic protein. It is not even evident that one can extrapolate to all tumor rejection antigens. One of skill in the art would then turn to the state of the art which has proven to be of an unpredictable and new status. To date, gene therapy, in general, is unpredictable, including genetic immunization involving short-term

expression of the therapeutic protein. For example, see Orkin et al. as cited in the last Office action on page 8. Thus, without specific guidance demonstrating the in vivo production of antigenic proteins in cells of a human and in view of the general state of gene therapy, the skilled artisan would have required an undue amount of experimentation to practice the claimed invention without a reasonable expectation of success.

Applicants assert that the examples disclosed in the specification "clearly support every step recited in the claims and the results achieved by these steps" (page 3 of the Amendment). However, the Examiner disagrees. For example, the examples are directed to a specific mouse tumor model, the B16 melanoma and OVA presentation in the C57 BL/6 mouse. Applicants assert that "OVA is representative of all of the other antigens disclosed in the application" (page 4 of the Amendment); however, do not present any data indicating this is true. The Examiner acknowledges the data presented in Exhibit II of the Declaration (page 1125, Figure 4) indicating the use of the "humanized" reporter gene encoding GFP; however, the use of two antigens does not sufficiently enable all antigens. It is not evident that similar results can be obtained by using any other DNA encoding an antigenic protein in the same mouse tumor model or any other mouse tumor model. Likewise, Applicants assert that the "OVA antigen used in this model is the same as that of many naturally occurring tumor antigens," thus "the results obtained here are applicable to a wide variety of tumors" (page 5 of the Amendment). However, Applicants do not demonstrate or provide data indicating that this is true. It is not evident that similar results can be applicable to other naturally occurring tumors in the mouse or in any other mammal. The

Examiner agrees that the Applicants demonstrate delivery of a specific particulate polynucleotide to the C57 BL/6 mouse and expression of OVA in the mouse which provided protection from injections of MO4 melanoma. However, to date, it is well known in the art that successful gene transfer and expression are muti-factorial in regard to the specific nucleotide sequence, the specific promoter, enhancer, coding sequences, non-coding sequences used in the construct; the specific vector; the site of integration; the specific host, etc. In view of this and the lack of specific guidance provided in the specification indicating successful genetic immunization in humans using additional antigenic proteins, the skilled artisan would have required an undue amount of experimentation to have practiced the entire claimed invention without a reasonable expectation of success.

Applicants comment that the prior Office action indicates a deficiency in support of many aspects of the claimed invention (page 4 of the Amendment). The Examiner maintains this view. For example, since other antigens are not well known or characterized, even if they can be readily introduced and expressed in the mammalian host, it is unpredictable that they will elicit an immune response. It is well known in the immunology art that the expression of antigens does not guarantee an immune response. Since the method is directed to immunization, Applicants must enable the entire claimed invention by showing the mammal is immunized against the specific antigen. In addition, the claims should recite that the expression of the antigen results in protective immunity. Thus, in view of the lack of guidance provided by the specification and the

unpredictability of the art, the claimed invention would have required an undue amount of experimentation without a reasonable expectation of success.

Applicants assert that "it is well established that animal models can be used to demonstrate efficacy for other mammalian hosts, including humans." However, the Examiner disagrees. The general state of the art indicates a considerable difference in mouse tumor models as compared to clinical trials so that it would be difficult to extrapolate results obtained from a mouse model to results obtained in clinical trials. For example, see Hanania et al. cited on pages 7-8 of the last Office action. In addition, there is no well-known, art-recognized, predictive animal model which exists for demonstrating the efficacy or therapeutic effect of Applicants' claimed method. Thus, the skilled artisan would have required an undue amount of experimentation to practice the claimed methods resulting in a therapeutic effect without a reasonable expectation of success.

Most importantly, the specification fails to provide specific guidance to practice any of the specific claimed methods. The specification discloses the claimed invention as methods of therapeutic or prophylactic genetic immunization in a patient by introducing particulate polynucleotides encoding a biologically active antigenic gene so that the cell expresses the antigenic protein thereby inducing tumor immunity, viral immunity, etc.; i.e., gene therapy. However, the specification fails to provide an enabling disclosure for gene therapy. For example, the specification fails to teach how to make and use a pharmaceutical composition comprising a particulate polynucleotide encoding a biologically active antigenic gene having a "therapeutically effective amount" useful for inducing tumor or viral immunity in a patient. The specification also

fails to teach a route and time course of administration of the therapeutic composition. Gene therapy is a highly unpredictable and undeveloped field and the skill in the art is high. See (Orkin et al., 1995) which states:

> 2. While the expectations and the promise of gene therapy are great, clinical efficacy has not been definitely demonstrated at this time in any gene therapy protocol, despite anecdotal claims of successful therapy and the initiation of more than 100 Recombinant DNA Advisory Committee (RAC)-approved protocols.
> 3. Significant problems remain in all basic aspects of gene therapy.

Furthermore, the specification lacks any working examples or specific teachings demonstrating that the therapeutic composition would deliver the appropriate nucleic acids to the appropriate target cells so that gene therapy would be therapeutically beneficial to a subject such as a human. The specification fails to show the regulation of a transferred therapeutic gene under physiological conditions. Would the gene be transiently expressed and not have therapeutic value or would the gene be overexpressed and lead to deleterious effects? Thus, one of skill in the art with respect to gene therapy and in view of the lack of guidance provided by the specification, would have required undue experimentation to have practiced the claimed methods of genetic immunization without a reasonable expectation of success.

As a final note, Applicants seem to suggest that the route of administration, particle bombardment, is essential for the success of the claimed methods (page 8 of Amendment). It is not evident that similar results can be obtained via a different route of administration. Thus, Applicants claimed method should be limited to particle bombardment since it's the only demonstrated effective method for delivery. Thus, in view of the lack of guidance provided by the

specification and the breadth of the claimed invention, one of skill in the art would have required an undue amount of experimentation to practice the entire claimed invention without a reasonable expectation of success.

2. Claim 59, newly amended, remains rejected under 35 U.S.C. §112, second paragragh, as set forth on pages 9-10 of the last Office action, because it remains vague and indefinite. The claim does not recite an intended result due to the expression of the antigenic protein(s) at "biologically effective levels". What is the intended result? Is it tumor or viral immunity, tumor regression? In addition, step (a) is unclear because it recites "a DNA fragment(s)". The specification fails to disclose or define the claimed methods using more that one DNA fragment at a time which express more than one antigen.

3. The rejection of claims 1-67 under 35 U.S.C. §103 as being unpatentable over Nabel et al. taken with Eisenbraun et al. and further in view of Robinson et al. is withdrawn in view of Applicants' arguments in the Amendment filed on Jan. 10, 1997.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

Jasemine C. Chambers

JASEMINE C. CHAMBERS, PHD.
SUPERVISORY PATENT EXAMINER
GROUP 1800

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jill Schmuck whose telephone number is (703)305-2147.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasemine C. Chambers, can be reached on (703)308-2035.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703)308-0196.

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1819.

Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703)308-0294.

Jasemine C. Chambers

JASEMINE C. CHAMBERS, PHD.
SUPERVISORY PATENT EXAMINER
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Jill Schmuck

February 29, 1997